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08/736,267

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
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EXAMINER
DUFFY, P

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JANIS K FRASER
RISH & RICHARDSON
225 FRANKLIN STREET
BOSTON MA 02110-2804

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on Jan 26, 1998.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-23 and 26-60 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-22 and 26-60 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 19 & 23 Filed on 14, 1997 and 3-17-98 Respectively

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

...ACTION ON THE FOLLOWING...

Response to Amendment

1. The Group and/or Art Unit of U.S. Patent application S.N. 08/736,267 has changed. In order to expedite the correlation of papers with the application please direct all future correspondence to Technology Center 1600, Group 1640, Art Unit 1645.

2. The amendment filed January 26, 1998 has been entered into the record.

3. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Rejections Withdrawn

4. The rejection of the claims over Platz et al under 102(e) is withdrawn because oleic acid is a liquid at room temperature and thus the alleged composition would not be a dry powder. One of skill in the art would have been readily aware that oleic acid was a liquid at room temperature and whereas oleic acid salts are solid powders at room temperature.

5. The rejection of the claims over Rubsamen under 103 is withdrawn because oleic acid is a liquid at room temperature and thus the alleged composition as combined would not be a dry powder. One of skill in the art would have been readily aware that oleic acid was a liquid at room temperature and oleic acid salts are solid powders at room temperature and thus the combination of the lyophilized polypeptide and oleic acid, can not meet the claimed criteria of the mixture being a dry powder composition.

6. All other previous objections and rejections are moot in view of the new grounds of rejection set forth below.

New Rejections

Double Patenting

7. The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 1-3, 11-16, 17-20 and 33-49 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-33 of U.S. Patent No. ~~5,581,998~~ 5518996. Although the conflicting claims are not identical, they are not patentably distinct from each other because the therapeutic composition of insulin in a dry powder composition comprising the enhancer and devices containing the composition anticipate the instant genus claims.

N.B. PAD

9. Claims 21, 22, 28-32 and 51-60 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 5,506,203. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of delivering the therapeutic composition of insulin in a dry powder composition comprising the enhancer to the lower respiratory tract anticipates the method of delivery by inhalation of the pharmaceutical compositions of the instant claims.

Specification

10. The title and abstract of the invention are not descriptive. A new title and abstract are required that is clearly indicative of the invention to which the claims are directed.

Claim Rejections - 35 USC § 112

11. Claims 1-22 and 26-60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition comprising insulin or C-peptide of insulin and an enhancer compound which has a consistency that permits it to be processed into primary particles having a diameter less than 10 microns, said composition in the form of a dry powder, methods of administration of the pharmaceutical composition and devices containing the pharmaceutical composition, it does not reasonably provide enablement for generic pharmaceutical polypeptides set forth in the claims, methods of administration or devices containing the pharmaceutical composition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to pharmaceutical compositions comprising a pharmaceutically active polypeptide and an enhancer compound which has a consistency that permits it to be processed into primary particles having a diameter less than 10 microns, said composition in the form of a dry powder, methods of delivering the compositions and devices containing the compositions. The claims include a multiplicity of polypeptides including hormones, vasopressin, desmopressin, glucagon, corticotropin, gonadotropin, luteinizing hormone, calcitonin, C-peptide of insulin, parathyroid hormone, human growth hormone, growth hormone, growth hormone releasing hormone, oxytocin, corticotropin releasing hormone, somatostatin, gonatogropin

agonist, human atrial natriuretic peptide, human thyroxine releasing hormone, follicle stimulating hormone, prolactin, growth factors, interleukin, polypeptide vaccine, enzyme, endorphin, glycoprotein, lipoprotein, and polypeptides involved in the blood coagulation cascade. The determination of undue experimentation in a given application requires the application of a reasonable evaluation taking into consideration the nature of the claimed invention and the state of the art. *Ex parte Forman et al.* 230 USPQ 546 summarizes the factors and criteria to be evaluated in order to determine if there is sufficient enabling written disclosure as to how to make and use the claimed invention. These factors include: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented in the specification, (c) the presence or absence of working examples, (d) the nature of the invention, (e) the relative skill of those in that art, (f) the predictability or unpredictability of the art, and (g) the breadth of the claims. The teachings of the specification are limited to how to make pharmaceutical compositions. With the sole exception of insulin and the C-peptide of insulin, the specification completely fails to teach how to *use* the plethora of pharmaceutical compositions to treat diseases, as is implicit in the pharmaceutical compositions and methods of delivering pharmaceutical compositions. The specification provides no written description of any disease which can be treated by these plethora of claimed polypeptides. The specification lacks any written description of any *in vivo* assay by which one skilled in the art could ascertain effective disease therapy for any of the plethora of pharmaceutical polypeptide compositions claimed. The single working example of an *in vivo* assay is the measurement of glucose levels, an assay which is specific for diabetes and insulin. This assay can not predictably and reproducibly measure the therapeutic effect of these other plethora of compounds for any other disease. The nature of the invention is drawn to the area of highly complex therapeutic arts where disease

treatment varies on location of target tissues, method and route of administration, dosage of administration, and composition *per se*. Not only does the specification lack a teaching of which diseases can be treated with the corresponding polypeptides, the specification fails to teach that inhalation with the instant pharmaceutical composition can effectively achieve dosages which have been demonstrated to be therapeutic. Assuming *arguendo* that one or more of the polypeptides have been used to pharmaceutically treat disease by an intravenous route. Merely because a polypeptide can be delivered intravenously at very high dosages, it does not logically follow that the same therapeutic dosage can be delivered to the lungs to achieve the same effective dosage. Thus, the *in vitro* assay which demonstrates enhanced traversal of the polypeptide across endothelial cells of the lung does not speak to the therapeutic dosage which can be delivered by this route, and does not speak to any therapeutic effect of the polypeptide delivered by this route. Consequently, it is not apparent that pharmaceutically effective dosages of the various polypeptides claimed can be delivered via inhalation, for any known disease. In view of the complete lack of written description of diseases which can be treated using the claimed polypeptides, the lack of written description of *in vivo* assays to test the therapeutic effectiveness for inhalation of the composition, the skilled artisan would be forced to independently develop assays for testing effective dosages for treatment non-disclosed diseases, and in the absence of further guidance from applicants, the skilled artisan would be forced into undue experimentation to use the pharmaceutical compositions, methods of delivery and devices containing the pharmaceutical compositions, in the absence of factual evidence to the contrary.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

13. Claims 1-13, 17- 20, 31-44, 48, and 49 are rejected under 35 U.S.C. 102(e) as being anticipated by Illum (U.S. Patent No. 5,707,644, filed May 21, 1993).

Illum teaches a dry microparticle composition comprising microparticles of more than 0.1 um in diameter but less than 10um, a drug including: insulin, enkephalins, LHRH and analogues, growth hormones, calcitonins, interferons, atrial natriuretic peptide, vasopressin and analogues, granulocyte-colony stimulating factor, thyrotropin releasing hormone, ACTH and analogues etc. (see column 7 line 26 - column 8, line 12) and an absorption enhancer (i.e. lyosophospholipids, acyl carnities, chelating agents, surface active agents, acyl glycerols, fatty acids and their salts, tyloxapol and biological detergents listed in the SIGMA catalogue, 1988, pages 316-321, enamines, malonates, salcylates, bile salts and analogues and fusidates). Illum teaches administration to the respiratory tract (column 9, first full paragraph) using dry powder inhaler devices which produces a finely divided clouds of the dry powder or microspheres (i.e. the instant particle). Thus, Illum is deemed to anticipate the instant compositions and devices.

14. Claims 1, 3-12, 17, 19, 20, 21, 26, 27, 28, 34-43 and 50-56 are rejected under 35 U.S.C. 102(b) as being anticipated by Durrani et al (WO 91/16882, published 14 November 1992).

Durrani et al teach spray dried bulk powder compositions comprising polypeptides (i.e. insulin, interleukin-2, lipocortinin, oxytocin, vasopressin, epidermal growth factor and termor necrosis factor; see page 43 claim 15), enzymes, enzyme inhibitors, allergens (page 10, first full paragraph) and at least one lipid or their analogues selected from the group consisting of phosphatidylcholine, phosphatidylinositiol, phosphatidic acid, phosphatidylethanolamine (see page 41, claim 4). The dry powder composition suitable for inhalation by either dry powder inhalers or suspended in a fluorocarbon propellant (page 6, lines 4-29). Durrani et al teach that the dried powder liposomes hade a bimodal distribution with two peaks one at 1 micron and at 7-10 microns. Durrani et al teach that the optimal size of dried liposomes for respirable particles is less than about 5 microns. Durrani et al teach that the majority of the particles of the powder fall well within this range (see paragraph bridging pages 14-15). Durrai et al teach both metered dose repetitive inhalers and single packet delivery inhalers for delivery of the liposome composition (see paragraph bridging pages 16-19).

15. Claims 1, 3-12, 17, 21, 26, 27, 34-43 and 50-56 are rejected under 35 U.S.C. 102(b) as being anticipated by Schipper et al (Pharmaceutic Research, 10(5):682-686, published May 1993).

Schipper et al teach nasal insulin delivery with dimethyl-β-cyclodextrin as an absorption enhancer in which the powder is more effective than liquid formulations in patients (i.e. rabbits). Schipper et al teach the administration of dry powders of insulin and dimethyl-β-cyclodextrin as an absorption enhancer, using a single dose insufflator (page 683, column 2, Figure 1). Thus,

the dry powder composition inherently anticipates the instant composition claims, devices and methods of administration.

Status of Claims

16. All claims stand rejected.

Conclusion

17. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Monday-Friday from 6:30 AM to 3:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached at (703) 308-4310.

Patricia A. Duffy, Ph.D.
April 26, 1998

Patricia A. Duffy

Patricia A. Duffy, Ph.D.
Primary Examiner
Group 1640